# A NEW SYNTHESIS OF CINNAMIC ACIDS FROM AROMATIC ALDEHYDES AND N,N-DIMETHYLACETAMIDE HYDROCHLORIDE

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Received February 6, 2007

Cinnamic acids have been prepared in 61-85% yields by a new synthesis from aromatic aldehydes and *N*,*N*-dimethylacetamide hydrochloride as reagent and solvent, at reflux (190-200°C), for 8-12 hours. Without *N*,*N*-dimethylacetamide hydrochloride this reaction is not possible.

## **INTRODUCTION**

Thorough studies of organic chemistry have emphasized the important role of reactive solvents in some condensation reactions, such as ethynylation of carbonylic compounds.<sup>1,2</sup> Some of the most widely used reactive solvents for these reactions are N,N-dialkylacetamides, among which N,N-dimethylacetamide is prominent due to its particular reactivity. This is the reason why it had been used not only as solvent and reaction medium,<sup>3,4</sup> but also as a very effective catalyst<sup>5</sup> and, in the case of N,N-dimethylacetamide hydrochloride, even as a reagent.<sup>6-9</sup> As a general feature, these reactive solvents are able to yield in compounds which result from a condensation reaction at the methylene group in  $\alpha$  position towards amide moiety, position activated by the presence of an electron withdrawing functional group (-E). The reactions of N,N-dimethylacetamide with aromatic ketones in the presence of strong bases such as potassium hydroxide (KOH) or sodium amide (NaNH<sub>2</sub>) as condensing agents are known.<sup>2</sup> Therefore, we considered of interest the condensation to study reaction of N.N-dimethylacetamide and aromatic aldehydes in the presence of a strong acid, such as hydrochloric acid (HCl).

On the other hand, the cinnamic acid and its derivatives, as reagents for organic and macro-molecular chemistry,<sup>10-14</sup> due to their photoreactive

character determined by the presence of the cinnamoyl group, as well as key components of a wide variety of pharmacological formulations, due to their flavouring abilities, antibacterial, antifungal and parasite fighting properties, still attract much attention from the scientific community.

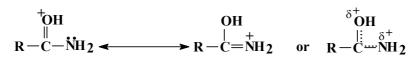
Despite of the great variety of well-known and tried methods (Perkin reaction,<sup>15</sup> Knoevenagel condensation,<sup>16</sup> Claisen condensation,<sup>17</sup> and Heck reaction<sup>18</sup>), the development of new general synthetic protocols for cinnamic acids is still an active field, where we do have some recent contributions concerning designed syntheses of cinnamic acids.<sup>19-21</sup>

In this paper, we present a new approach of the cinnamic acids synthesis, starting from aromatic aldehydes and *N*,*N*-dimethylacetamide hydrochloride as reagent and solvent. The protocol of this new method and a study of optimization on reaction parameters are presented herein.

## **RESULTS AND DISCUSSION**

As generally known, amides are weak bases, even weaker than the amines due to the fact that the doublet from nitrogen atom is delocalized on many atoms. As result, they can react with acids, yielding in amides preferably protonated at the oxygen atom, stabilized by conjugation, as presented in Scheme 1.

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Scheme 1 - Resonance structures of a protonated amide.

If the protonation would take place at the nitrogen atom, the conjugation would suppressed. Even more, the amide protonated at the oxygen atom is more stable than the initial amide, due to its lower energy.<sup>22</sup> Protonation of the amide carbonyl makes the carbon atom more electrophilic.

The carbonyl functional group is a stronger dipole compared to N-C moiety due to the double bonding C=O and to the specific distribution of  $\pi$ electrons at the oxygen atom which gives oxygen atom a higher electronegativity. The presence of a

C=O dipole and, to a lesser extent a N-C dipole, allows amides to act as  $H^+$  acceptors.

Under these circumstances, by stepwise investigation, we established that aromatic aldehydes I can react with N,N-dimethylacetamide hydrochloride as reagent, in the mole ratio 1:4, resulting in cinnamic acids II and dimethylamine as by-product, as presented in Scheme 2.

The final products were obtained in good yields, after purification, and were identified by melting point measurements and IR and <sup>1</sup>H-NMR spectroscopy. All experimental data obtained are summarized in Table 1.

R <sup>1</sup> C <sub>6</sub> H₄CHO I		1) H <sub>3</sub> CCON(CH <sub>3</sub> ) <sub>2</sub> •H 2) H <sub>2</sub> O, NaOH			$\rightarrow$ R <sup>1</sup> C <sub>6</sub> H <sub>4</sub> CH=CHCOOH II			+ HN(CH	[3)2	
F	ξ1	<i>p</i> -Cl	<i>р-</i> Н	<i>m</i> -Cl	<i>p</i> -NO <sub>2</sub>	<i>m</i> -NO <sub>2</sub>	<i>p</i> -СН3О	o-NO <sub>2</sub>	<i>р</i> -СН3	_
	I	Ia	Ib	Ic	Id	Ie	If	Ig	Ih	

Scheme 2 – Synthesis of cinnamic acids in the presence of *N*,*N*-dimethylacetamide hydrochloride.

Cinnamic acids obtained in the presence of *N.N*-dimethylacetamide hydrochloride

Cinnamic acids <sup>a</sup>	Yields <sup>b</sup> (%)	Reaction time (h)	m.p. <sup>c</sup> (°C)	Literature m.p. (°C)
IIa	85	8	248-250	249-250 <sup>23</sup>
IIb	67	10	131-133	132-133 <sup>24</sup>
IIc	84	8	176-177	175-177 <sup>23</sup>
IId	81	9	285-286	284-286 <sup>25</sup>
IIe	79	10	196-197	195-197 <sup>26</sup>
IIf	61	12	174-175	173-175 <sup>24</sup>
IIg	78	8	237-239	237-239 <sup>25</sup>
IIĥ	64	12	196-198	197-198 <sup>23</sup>

Table 1

<sup>a</sup> The cinnamic acids obtained were identified by comparison of their m.p. and IR and <sup>1</sup>H-NMR spectra with authentic samples.

<sup>b</sup> Yields calculated based on the aromatic aldehydes I employed.

<sup>c</sup> After recrystallization.

A study of optimization was performed in order to establish the influence of various factors, such as chemical structure of the reagents, stoichiometry, time and temperature, on the reaction yield.

The first conclusion of our study is that this new synthetic pathway is not valid for aliphatic aldehydes, due to their lower reactivities. Moreover, if the reagent N,N-dimethylacetamide hydrochloride is replaced by N,N-dimethylacetamide, the reaction does not take place, which demonstrates the key role of this compound.

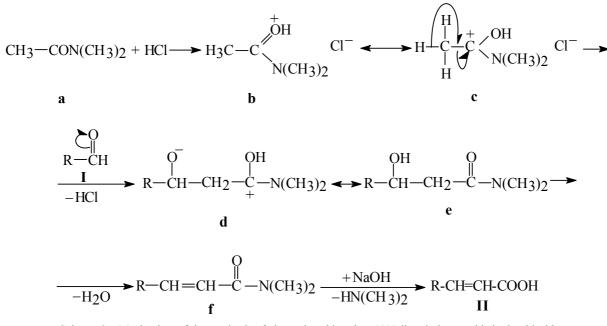
Regarding the stoichiometry, the molar ratio between I and N,N-dimethylacetamide hydrochloride should be 1:1. Practically, the molar ratio we used was 1:4, which provided good vields, considering that N,N-dimethylacetamide hydrochloride acts also as solvent for this reaction mixture. Using the stoichiometric ratio of 1:1, the yields decreased. For example, the yield for product IIa decreased to 24-30% when the reaction was performed in a mole ratio of 1:1. So, for better results, an excess of N,N-dimethylacetamide hydrochloride is required.

This synthesis requires high temperatures (reflux at 190-200°C), during 8-12 hours (Table 1). At lower temperatures, the yield decreases. For example, the yield for product **IIb** decreased to 45% when the reaction was performed at 130-140°C. Same decrease was observed when the reaction time was reduced to 7 h.

As presented in Table 1, we obtained cinnamic acids **II** in yields which ranged from 61 to 85%, yields determined by the reaction conditions and

structure of the aromatic aldehydes I employed. The cinnamic acid IIf has been obtained in the lowest yield due to the presence of p-CH<sub>3</sub>O group which has an electron-donating (+E) effect. Cinnamic acids with electron-withdrawing (-E) substituents were obtained in good yields.

Taking into account the theoretic features presented herein, it is possible to suggest a mechanism for this synthesis, presented in Scheme 3.



Scheme 3 – Mechanism of the synthesis of cinnamic acids using N,N-dimethylacetamide hydrochloride.

It involves the reaction of *N*,*N*-dimethylacetamide with the hydrochloric acid, (a) when N,N-dimethylacetamide hydrochloride (b) results in situ, reagent which has a reactive methylene group activated by the adjacent carbon atom (structure c) deficient in electrons, an interesting phenomenon yet unsufficiently studied in the case of protonated amides. This reagent reacts with the aromatic aldehydes I, resulting in cinnamic acids **II**, after the alkaline hydrolysis of intermediate (**f**) in the presence of NaOH solution, as presented in Scheme 3.

## **EXPERIMENTAL**

#### **Reagents and materials**

All reagent-grade aromatic aldehydes were purchased from Sigma Aldrich Co. and used as received. *N*,*N*-dimethylacetamide is commercially available (Fluka) and it was anhydrized prior to use by vacuum distillation over calcium hydride and stored over molecular sieves (4Å).

#### Measurements

The IR absorption spectra were recorded on a Carl Zeiss Jena SPECORD M80 spectrophotometer on KBr pellets. The <sup>1</sup>H-NMR spectra were run using a Jeol C60-HL spectrometer with DMSO-d<sub>6</sub> as solvent and tetramethylsilane as internal standard. The melting points were measured with a Gallenkamp hot-block melting point apparatus.

#### General procedure for the synthesis of cinnamic acids

In a 100 mL three-necked Claisen flask, 3.72 mL (0.04 mole) N,N-dimethylacetamide and 7 mL benzene were added. Then, gaseous hydrogen chloride was passed through this solution for 45-60 min, when N,N-dimethylacetamide hydrochloride precipitated. 0.01 Mole of aromatic aldehyde I was added and the obtained mixture was heated for 8-12 h at 190-200°C, while benzene distilled (see Table 1). At the end of the reaction, the final solution was treated with 50-60 mL water and then with NaOH solution 20% to pH=9-10. From this solution, the unreacted aromatic aldehyde I was distilled with water under vacuum (30-40 mmHg) until the distillate was no longer cloudy. The solution was diluted with water until a volume of 70-80 mL; then, 10-15 mL NaOH solution 20% was added. This mixture was refluxed until the amide precipitate disappeared by hydrolysis (5-6 h). After cooling at room temperature, this solution was filtered and the filtrate

was treated with HCl solution 15-20%, until pH=1-2, when the cinnamic acid II precipitated. The obtained product was filtered, washed with 10-15 mL cold water and dried. Yields ranged from 61 to 85% (Table 1).

## CONCLUSION

A novel synthetic pathway for obtaining cinnamic acids in good yields from aromatic aldehydes and N,N-dimethylacetamide hydrochloride has been identified. The key compound of this synthesis, N,N-dimethylacetamide hydrochloride, is not only a solvent for this reaction system, but a very effective reagent, fact proved by the impossibility to perform this reaction in its absence. This new alternative route is not suitable for aliphatic aldehydes. The synthesis yield depends on the reaction conditions. The mechanism we propose evolves through an intermediate which has a reactive methylene group activated by the adjacent carbon atom of the protonated amide. This method is a very effective alternative to the classic Perkin synthesis.

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